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Pediatrics 2010;125:e925-e930; originally published online Mar 29, 2010;

DOI: 10.1542/peds.2009-2382

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located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/125/4/e925>

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American Academy of Pediatrics

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Gastroesophageal Reflux and Asthma in Children: A Systematic Review

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KEY WORDS

gastroesophageal reflux, asthma, reflux, review

ABBREVIATIONS

GERD—gastroesophageal reflux disease

OR—odds ratio

CI—confidence interval

ATS—American Thoracic Society

This study was completed independent of financial support from any specific sponsor, and the authors are solely responsible for the study design, collection, analysis, and interpretation of the data, and the writing of the report.

www.pediatrics.org/cgi/doi/10.1542/peds.2009-2382

doi:10.1542/peds.2009-2382

Accepted for publication Nov 10, 2009

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

abstract

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CONTEXT: The relationship between gastroesophageal reflux disease (GERD) and asthma in children has been investigated; however, the nature of the association (if any) between these 2 conditions is unclear.

OBJECTIVE: We performed a systematic review of the literature to examine the association between GERD and asthma in children.

METHODS: A search of the medical literature was conducted by using PubMed and Embase (1966 through December 2008). Full-length articles in English that described at least 20 subjects younger than 18 years were included if they reported the prevalence of GERD (symptoms, pH studies, endoscopy/histology) in individuals with asthma or the prevalence of asthma in individuals with GERD. We calculated pooled odds ratios from studies that examined control groups, and we pooled prevalence estimates from all studies.

RESULTS: A total of 20 articles that described 5706 patients fulfilled the inclusion and exclusion criteria. Seventeen studies used objective methods for documenting reflux (eg, pH probe, contrast imaging, impedance, esophagogastroduodenoscopy), 2 studies relied on symptom-based questionnaires, and 1 study used diagnostic codes. Most studies ($n = 19$) examined the prevalence of GERD in 3726 individuals with asthma and reported highly variable estimates (19.3%–80.0%) and a pooled average of 22.8% with GERD symptoms, 62.9% of 789 patients with abnormal esophageal pH, and 34.8% of 89 patients with esophagitis. Only 5 studies included controls and enrolled 1314 case-patients with asthma and 2434 controls without asthma. The average prevalence of GERD was 22.0% in asthma cases and 4.8% in controls (pooled odds ratio: 5.6 [95% confidence interval: 4.3–6.9]).

CONCLUSIONS: There is a possible association between GERD and asthma in pediatric patients seen with asthma in referral settings. However, because of methodologic limitations of existing studies, the paucity of population-based studies, and a lack of longitudinal studies, several aspects of this association are unclear. *Pediatrics* 2010;125:e925–e930

Many studies and numerous reviews have attempted to define the relationship between gastroesophageal reflux disease (GERD) and asthma in children. However, the nature of the relationship is uncertain. We recently completed a systematic review of published studies of adults and found that the average prevalence of GERD symptoms in patients with asthma is close to 60%.¹ In adults, an association between GERD and asthma has been consistently reported in published studies, but the direction of causality remains unclear.¹ Although several pieces of evidence for an association between GERD and asthma have been critically reviewed in adult studies, such work does not exist for pediatric studies.

Therefore, we conducted a systematic review of the literature to provide an estimate of the prevalence of abnormal esophageal findings (eg, abnormal pH, hiatal hernia, inflammation) in children with asthma. We also aimed to determine the magnitude of the association between GERD and asthma and their temporal relationship in children.

METHODS

Literature Search

We searched the medical literature for studies that examined the association between asthma and GERD in children by using Medline (PubMed), Embase (Scopus), and the Cochrane Library databases from 1966 to 2008. Articles were identified with the Medical Subject Heading (MeSH) and free-text terms “reflux,” “GERD,” “esophagitis,” or “hiatal hernia” (all MeSH and free-text terms). Using the set operator “and,” we combined these articles with studies that evaluated asthma by using the term “asthma.” PubMed was used to search Medline, and Scopus was used to search Embase. The bibliographies of pertinent articles were also reviewed for relevant articles.

Selection Criteria and Analysis

All full-length articles in English were included if the study (1) assessed the prevalence or incidence of GERD in individuals with asthma, (2) assessed the prevalence or incidence of asthma in individuals with GERD, (3) reported the prevalence of abnormal esophageal acid exposure in children with asthma, or (4) reported the prevalence of positive endoscopic findings in children with asthma. We excluded studies that examined participants older than 18 years, had a sample size of <20, or studied nonasthma respiratory conditions including reactive airway disease, asthma-like airway disease, chronic cough, recurrent pneumonia, infantile apnea, or stridor. We excluded the terms “reactive airway disease” and “asthma-like airway disease” to reduce variability of disease definition in our cohort. Relevant studies were assessed by 2 reviewers for inclusion in the review on the basis of the criteria listed above. The data extracted from each article included the year and country of enrollment, study design, number of participants, method of reflux or asthma

assessment, and prevalence of reflux or asthma symptoms in controls. Abstracted data included prevalence of Barrett’s esophagus, abnormal esophageal pH, hiatal hernia, or esophagitis among study participants.

We determined overall prevalence estimates by pooling the values from studies that met the selection criteria and calculating sample-size-weighted mean values. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained and/or calculated for studies that enrolled controls. The following quality criteria were identified in each study: (1) consecutive recruitment of participants; (2) outcome measurements; and (3) identification and adjustment for confounders.

RESULTS

A total of 1562 articles were retrieved on the basis of the general search strategy (Fig 1). Review of titles and abstracts revealed 44 articles that examined pediatric asthma or GERD. A detailed manual review of the manuscripts revealed that 20 articles fulfilled the inclusion and exclusion criteria (Tables 1 and 2). Of these, 19 studies examined the prevalence of

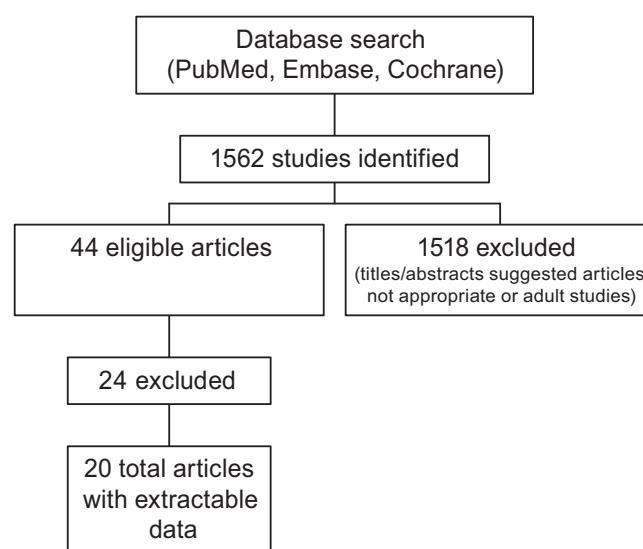


FIGURE 1
Literature-search strategy.

TABLE 1 Pediatric Studies that Examined GERD in Individuals With Asthma Compared to Controls Without Asthma

Author (Year), Location	Age, y	Study Design	Sample Size, N	Consecutive Enrollment	Method of Reflux Assessment	Prevalence of Reflux in Patients With Asthma, n/N (%)	Prevalence of Reflux Symptoms in Controls, n/N (%)	Unadjusted OR (95% CI)	Prevalence of Abnormal Esophageal pH, n/N (%)
Petersen et al ¹⁴ (1989), Denmark	Median: 8	Prospective	24	NR	Barium	8/24 (33.3)	1/15 (6.7)	7.0 (0–22.4)	NA
Gustafsson et al ⁸ (1990), Sweden	Mean: 13.7	Prospective	42	NR	pH probe	21/42 (50.0)	4/27 (14.8)	5.2 (1.5–26.2)	21/42 (50.0)
Chopra et al ³ (1995), India	Mean (SD): 6.6 (3.7)	Prospective	80	NR	Radionuclide scan	31/80 (38.8)	0/10 (0.0)	13.4 (1.3–135.8)	NA
Debley et al ¹⁶ (2006), United States	Median: 13–14	Population based	1806	NA	Questionnaire	57/296 (19.3)	38/1510 (2.5)	9.2 (5.9–14.6)	NA
Størdal et al ⁶ (2006), Norway	Mean: 10.4	Prospective	872	NR	Questionnaire	172/872 (19.7)	74/872 (8.5)	2.6 (1.7–4.2)	NA

NR indicates not reported; NA, not applicable.

TABLE 2 Pediatric Studies That Examined GERD in Individuals With Asthma

Author (Year), Location	Age, y	Study Design	Sample Size, N	Consecutive Enrollment	Method of Reflux Assessment	Prevalence of Reflux, n/N (%)	Prevalence of Abnormal Esophageal pH, n/N (%)	Prevalence of Hiatal Hernia, n/N (%)	Prevalence of Esophagitis, n/N (%)
Friedland et al ¹⁵ (1973), United States	Mean (SD): 9.4 (1.8)	Prospective	54	NR	EGD	26/54 (48.1)	NA	26/54 (48.1)	NR
Berquist et al ²⁰ (1981), United States	Mean: 7.5	Retrospective	59	NR	Upper GI series, manometry, EGD	30/59 (51.2)	NA	NR	NR
Martin et al ⁹ (1982), United States	Mean: 9.6	Prospective	25	NR	pH probe	16/25 (64.0)	16/25 (64.0)	NA	NA
Andze et al ²¹ (1991), Canada	NR	Retrospective	139	NR	pH probe	105/139 (75.5)	105/139 (75.5)	NA	NA
Tucci et al ¹³ (1993), Italy	Mean: 6.3	Prospective	36	NR	pH Probe	27/36 (75.0)	27/36 (75.0)	NA	NA
Poder et al ¹² (1997), Hungary	NR	Prospective	25	NR	pH probe	13/25 (52.0)	13/25 (52.0)	NA	NA
Balson et al ² (1998), United States	Range: 2–17 y	Prospective	79	NR	pH probe	58/79 (73.4)	58/79 (73.4)	NA	NA
Cinquetti et al ¹⁰ (2002), Italy	Mean: 7.1	Prospective	77	NR	pH probe	47/77 (61.0)	47/77 (61.0)	NA	4/47 (8.5)
Khoshoo et al ²² (2003), United States	Mean (SD): 8.3 (1.3)	Prospective	46	Yes	pH probe	27/46 (58.6)	27/46 (58.6)	NA	NA
Gorenstein et al ²³ (2003), Israel	Mean (SD): 1.4 (2.8)	Retrospective	153	No	pH probe	64/153 (41.8)	64/153 (41.8)	NA	NA
Nijevitch et al ¹¹ (2004), Russia	Mean (SD): 13.2 (1.2)	Retrospective	42	NR	EGD	27/42 (64.3)	NA	0/42	27/42 (64.3)
Ay et al ⁴ (2004), Turkey	Mean (SD): 8.6 (4.5)	Prospective	36	NR	pH probe	27/36 (75.0)	27/36 (75.0)	NA	NA
Teixeira et al ¹⁵ (2007), Brazil	Mean: 2.6	Prospective	69	No	pH probe	47/69 (68.1)	47/69 (68.1)	NA	NA
Khoshoo et al ²⁴ (2007), United States	Range: 6–12 y	Prospective	62	Yes	pH probe	44/62 (80.0)	44/62 (71.0)	NA	NA

NR indicates not reported; NA, not applicable; EGD, esophagogastroduodenoscopy; GI, gastrointestinal.

GERD in patients with asthma (total of 3726 subjects), and 1 study examined the prevalence of asthma in patients with GERD (total of 1980 subjects). Most studies ($n = 14$) reported prospective collection of information. Fewer than half of the studies (8 of 20) were conducted in the United States.

Twelve studies measured esophageal pH, and 3 studies included endoscopic evaluation. The definition of asthma was not reported by most studies; only 5 studies provided criteria for asthma diagnosis, and only 1 study followed American Thoracic Society (ATS) criteria.^{2–6}

Only 5 studies enrolled control subjects; information on these studies is listed in Table 1. The pooled OR was 5.6 (95% CI: 4.3–6.9) for 5 studies that reported the prevalence of GERD symptoms in 1314 individuals with asthma compared with 2434 controls. Only 1 study was population based.

Overall, the prevalence of GERD in children with asthma ranged from 19.3% to 80.0%. The sample-size-weighted average prevalence of GERD in patients with asthma was 22.8% (847 of 3726). In patients with asthma, the average prevalence of abnormal esophageal pH was 68.2% (426 of 625) and of esophagitis was 35.6% (47 of 132). Of these studies, 2 reported using consecutive enrollment. Balson et al² followed ATS criteria and found a prevalence of 73.4% for GERD by using a pH probe.

One study that enrolled subjects with GERD ($n = 1980$) identified by *International Classification of Diseases, Ninth Revision* (ICD-9) codes reported the prevalence of asthma.⁷ The prevalence of asthma in individuals with GERD was 13.2%, whereas in controls it was 6.8%.

Studies That Reported Esophageal pH

We identified 12 studies that measured esophageal pH in children with asthma. The prevalence of abnormally high acid exposure ranged from 41.8% to 80.0%. The pooled sample-size-weighted average prevalence of abnormal esophageal acid exposure was 62.9% (496 of 789). The definition of abnormal high-esophageal-pH exposure was inconsistent among the studies. For example, 4 studies were performed by using a threshold of $\text{pH} < 4$ in distal esophagus for $>4\%$ of a 24-hour study, whereas 3 used a threshold of $>5\%$, 1 study used a threshold of $>6\%$, and 1 study used a threshold of $>1\%$.

Only 1 esophageal pH study, by Gustafsson et al,⁸ included a control group. The authors reported a prevalence of 14.8% abnormal acid exposure in 27 healthy children.⁸ Two studies also reported the prevalence of proximal (15 cm above the lower esophageal sphincter) abnormal esophageal pH and found abnormal acid exposure in 49% (57 of 116).^{2,8}

Two studies examined nocturnal asthma symptoms in children with asthma. In 1 study that examined 25 subjects, nocturnal asthma was associated with acid exposure⁹; however, the authors failed to find any association between nocturnal wheezing and abnormal pH in 77 subjects.

Studies That Reported Endoscopy Results

We identified 2 studies that enrolled a total of 89 children with asthma who underwent upper endoscopy.^{10,11} The authors of these studies reported a prevalence of endoscopic esophagitis of 15.7% and histopathological esophagitis of 64.3%.

Temporal Relationship Between GERD and Asthma

The temporal relationship between GERD and asthma was investigated in 3 cross-sectional studies that assessed whether respiratory symptoms followed episodes of GERD. The studies failed to show a consistent relationship between respiratory symptoms (wheezing, cough) and periods of abnormal esophageal pH or reflux symptoms. Specifically, 2 studies used esophageal pH-metry, and only 7 of 29 (24%) patients were reported to have asthma symptoms during depression of esophageal pH.^{8,9} The third study that examined only symptoms found that only 19.5% (15 of 77) of the patients with asthma had respiratory symptoms linked to possible reflux symptoms (vomiting, regurgitation).¹⁰ There have been no longitudinal studies that examined the association between a new diagnosis of asthma or GERD and the subsequent development of GERD or asthma.

Atopic Versus Nonatopic Asthma

Three studies specifically examined children with atopic asthma, defined by elevated serum immunoglobulin E level or reaction to allergens on a skin

test. Of the 3 studies, 2 used a pH probe to examine GERD in patients with asthma and revealed that there was no significant difference in prevalence between those with atopic versus nonatopic asthma.^{12,13} However, Petersen et al¹⁴ used a barium radiologic test and found that 8 children with nonatopic asthma had a higher prevalence of GERD compared with 15 control patients (62.5% vs 6.7%; $P < .01$).

Severity-Response Relationship

Four of the studies that evaluated GERD in patients with asthma examined the association between the severity of asthma and the presence or severity of GERD. Cinquetti et al¹⁰ found that children with more severe asthma had a significantly longer duration of abnormal pH. However, 2 other studies that used pH measurements revealed no significant difference in the prevalence of GERD between children with moderate and severe asthma.^{8,15} Debiley et al¹⁶ found that asthmatic children who required more frequent medical care (eg, physician visits, medications) had more frequent GERD symptoms.

DISCUSSION

Our systematic review included 20 observational studies that examined the association between asthma and GERD in children. The pooled OR for the association between GERD and asthma reported in the only 5 controlled studies was 5.6 (95% CI: 4.3–6.9). However, only 1 of these studies was population based, only 1 used recruitment of consecutive patients, and the studies used different definitions for asthma and GERD. The sample-size-weighted average prevalence of GERD in patients with asthma from 19 studies was 22.8%. We identified only 1 study that reported the prevalence of asthma in patients with GERD and reported a 13.2% prevalence and an OR of 2.1 (95% CI: 1.8–2.5) for the associa-

tion between asthma and GERD.⁷ There were several observational studies with results that supported a treatment-response relationship, but none of the studies had controls. We found no longitudinal studies and no consistent evidence for a severity-response relationship between asthma and GERD. Our findings support a possible association between GERD and asthma in children; however, we did not find enough evidence to support causality, and we identified multiple areas of deficiencies that require further study. The results of our study underscore the lack of evidence to support a clear association between GERD and asthma.

The risk estimate for the association between GERD and asthma in children is similar to that reported in a meta-analysis of studies of adults, which showed a pooled OR of 5.5 for studies that measured the prevalence of GERD in patients with asthma.¹ The average prevalence of GERD in patients with asthma seems to be lower in children (22.8%); studies of adults have revealed an average prevalence of 59.2%.¹ The prevalence of GERD in children with asthma varied widely (from 19.3% to 80.0%) in the included studies, reflecting small sample size, a different sampling frame for the studies, regional differences, and inconsistent methodologies used to define GERD.

The majority of studies that we reviewed ($n = 12$) measured esophageal pH in children with asthma to determine GERD prevalence estimates. However, only 1 study followed North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines for reporting the percentage of the total time with $\text{pH} < 4$ (the reflux index). It is thought to be the most valid measure of reflux

(upper limit of normal up to 12% in the first year of life and up to 6% thereafter).¹⁷ The majority of studies used a reflux-index threshold that was lower than that required by these evidence-based guidelines, which possibly led to an overestimation of the prevalence of reflux in patients with asthma. However, pH-metry is also limited by the inability to detect nonacid reflux.

A global, evidence-based consensus on the definition of GERD in the pediatric population suggests that GERD be defined by using a “patient-centered, symptom-based” method.¹⁸ In our review, the only 2 studies that included symptom-based methodologies to define GERD produced similar prevalence estimates (19.3% and 19.7%), and these estimates were the lowest among the included studies.^{6,16} Symptom-based techniques also have significant limitations in children, because verbal descriptions of symptoms may be unreliable until the age of 8 years, and older children may not be expressive during an office visit.¹⁸ In addition, symptoms suggestive of GERD are common in childhood, and it is difficult to determine which children actually have GERD.¹⁹

Although the overall prevalence of GERD and the pooled OR derived from the available studies imply an association between GERD and asthma, there are significant gaps in the evidence supporting a causal relationship. Most of the included studies were cross-sectional; just 1 study was population based.¹⁶ Only 5 studies enrolled control subjects. Only 3 studies evaluated the temporal relationship between the 2 diseases, and no longitudinal studies with long-term follow-up were available. In addition, there was only 1 study that explored the prevalence of

asthma in children with underlying GERD.

An association could be calculated from only 5 studies that enrolled control groups; of these studies, only 1 had a large sample size. The remaining studies were “prevalence” case series from which risk estimates could not be derived. The prevalence studies were mostly from referral centers; therefore, selection bias may exist. None were population or community based. The majority of studies did not include a precise definition of asthma. Only 1 study (Balson et al²) followed ATS criteria, and that study revealed a prevalence of 73.4% for GERD by pH probe. In contrast, the prevalence of GERD in all other studies was 21.6% (789 of 3647). In addition, definitions of GERD were inconsistent among the studies. The treatment studies were observational noncontrolled, which severely limits the inferences made about the reversibility part of the association between the 2 conditions.

CONCLUSIONS

The results of our systematic review suggest an association between GERD and asthma in pediatric patients who present with asthma in secondary and tertiary referral settings. However, there is a deficiency of evidence in several areas to support this association. The nature and direction of the association are unclear because of a lack of longitudinal studies establishing the correct temporal sequence, studies suggesting no severity-response relationship, and inadequate data supporting a treatment-response relationship. Our results emphasize the need for more epidemiologic studies, including long-term follow-up, to examine the relationship between GERD and asthma.

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